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SCHWEGMAN, LUNDBERG & WOESSNER, P.A.
P.O. BOX 2938
MINNEAPOLIS, MN 55402

EXAMINER	
HILL, KEVIN KAI	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/815,262	ENGELHARDT ET AL.	
	Examiner	Art Unit	
	KEVIN K. HILL	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 February 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9-27,29-46,48-53,55-59,61 and 62* is/are pending in the application.

4a) Of the above claim(s) *3,25-27,29-42,45,51-53 and 55-59* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-7,9-24,43,44,46,48-50,61 and 62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Applicant has elected with traverse the invention of Group I, Claims 1-32 and 43-60, drawn to a method of enhancing recombinant adeno-associated virus (rAAV) transduction in mammalian cells, comprising contacting the mammalian cells with at least one agent in an amount effective to additively or synergistically enhance rAAV transduction.

Within Group I, Applicant has further elected the restricted subgroup "A", wherein the at least two agents additively enhance rAAV transduction.

Within Group I, Applicant has elected the following species:

a) the agent interaction effect species "ii), wherein the agent alters cellular uptake of rAAV, as recited in Claims 4 and 46.

b) the biological functionality associated with an agent species "vi", wherein the agent modulates rAAV processing in the cell, as recited in Claims 28, 43 and 54.

c) the agent category species "xiii and xiv", wherein the agents are an antibiotic and a chemotherapeutic, as recited in Claims 8 and 47.

d) the biological functionality species "doxil" and "LLnL", as recited in Claims 21 and 60. However, upon further examination of the subject matter, the Examiner has extended the species under examination to include doxorubicin.

e) the cell type species "mammalian lung cell", as recited in Claims 16 and 48.

f) the polypeptide biological functionality species "cystic fibrosis transmembrane conductance regulator (CFTR)", as recited in Claim 20, wherein CFTR is found in both rAAVs.

Amendments

Applicant's response and amendments, filed February 4, 2008, to the prior Office Action is acknowledged. Applicant has cancelled Claims 8, 28, 47, 54 and 60, withdrawn Claims 3, 25-27, 29-42, 45, 51-53 and 55-59, amended Claims 1, 4, 21, 43 and 46, and added new claims, Claims 61-62.

The Examiner notes that cancellation of claims 28 and 54 removes the recitation of Applicant's elected biological functionality associated with an agent species "vi", wherein the agent "modulates rAAV processing in the cell".

Claims 3, 25-27, 29-42, 45, 51-53 and 55-59 are pending but withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim.

Claims 1-2, 4-7, 9-24, 43-44, 46, 48-50 and 61-62 are under consideration.

Examiner's Note

Unless otherwise indicated, previous objections/rejections that have been rendered moot in view of the amendment will not be reiterated. The arguments in the February 4, 2008 response will be addressed to the extent that they apply to current rejection(s).

Priority

Applicant's claim for the benefit of a prior-filed application parent provisional application 60/459,323, filed on March 31, 2003 and 60/512,347, filed on October 16, 2003 under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged.

Information Disclosure Statement

Applicant has filed Information Disclosure Statements on March 10, 2008, providing more than 200 references. The Examiner was able to consider these to the extent of time allowable. The signed and initialed PTO Forms 1449 are mailed with this action.

Specification

1. **The disclosure stands objected to because of the following informalities**:

The specification discloses that Figure 4B tabulates luciferase activity in HeLa cells infected rAAV, "and co-administration of…, or a combination of LLnL and doxorubicin" (pg 19, lines 26-30). However, none the figure legends of Figures 4A-E identify data from the combined use of LLnL and doxorubicin.

Figure 6 consists of three panels, A-C. However, the specification does not disclose the data presented in Figure 6C (pg 20, lines 6-10).

Figure 8 consists of three panels, A-C. However, the specification does not disclose which data is presented in its corresponding panel (pg 20, lines 13-16).

Figure 9 consists of four panels, A-D. However, the specification does not disclose which data is presented in its corresponding panel (pg 20, lines 17-23).

Figure 11 consists of four panels, A-D. However, the specification does not disclose which data is presented in its corresponding panel (pgs 20-21, joining ¶).

Figure 13 consists of two panels, A-B, wherein the specification discloses the data presented in the corresponding panels as "right panel" and "left panel". (pg 21, lines 18-23) However, there are no "right" or "left" panels. It would be remedial to correctly identify each panel by its Figure title: Figure 13A, Figure 13B.

Appropriate correction is required.

Response to Amendments

Applicant argues that the terms "doxorubicin" and "doxyrubicin" are synonymous, and that the active ingredient in DOXIL® is doxorubicin. Furthermore, in the context of the particular data disclosed in the specification (*in vitro* versus *in vivo*), the use of "DOX" in the specification is clear.

Applicant states that "DOX" employed to generate the data shown in Figures 7, 13, 17 and 19 is not DOXIL®, as such data was obtained *in vitro*; whereas, the "DOX" employed to generate the data shown in Figure 3C is DOXIL®. The "DOX" employed to generate the *in vivo* data shown in Figure 18 is doxorubicin.

Applicant's response appears to be directed to the Drawings filed March 31, 2004. However, Applicant's attention is directed to the **Drawings filed October 29, 2004** because they are the most recent amendment to the Drawings filed in the application considered by the Examiner and the quality of these Figures are significant improvements over the earlier-filed March 31, 2004.

The Examiner's objections were/are in reference to the Drawings filed October 29, 2004.

Applicant's amendments to the specification, specifically the Brief Description of the Drawings should be clearly concordant with the Drawings filed October 29, 2004, or any newly amended drawings submitted in response to this Office Action.

With respect to Figure 4, Applicant has not amended the Brief Description of the Drawings to better describe the data presented in Figures 4A, 4B, 4C, 4D and 4E. The specification discloses that Figure 4B tabulates luciferase activity in HeLa cells infected rAAV, "and co-administration of…, or a combination of LLnL and doxorubicin" (pg 19, lines 26-30). However, none the figure legends of Figures 4A-E identify data from the combined use of LLnL and doxorubicin.

With respect to Figure 6, Applicant has not amended the Brief Description of the Drawings to better describe the data presented in Figures 6A, 6B and 6C.

With respect to Figure 8, Applicant has not amended the Brief Description of the Drawings to better describe the data presented in Figures 8A, 8B and 8C.

With respect to Figure 9, Applicant has not amended the Brief Description of the Drawings to better describe the data presented in Figures 9A, 9B, 9C and 9D.

With respect to Figure 10, Applicant has amended the Brief Description of the Drawings to better describe the data presented in Figures 10A and 10B. It is unclear why Applicant has also replaced the annotations "A" and "B" with "upper" and "lower", respectively. Applicant is **strongly encouraged**, and it would be remedial, to replace "upper" and "lower" with "A" and "B" because "10A" and "10B" would clearly identify their corresponding figure panel regardless of how the plurality of figure panels are arranged when printed; whereas, the identity of "upper" and "lower" can easily change upon re-arrangement of figure presentation, thereby obfuscating the disclosure.

With respect to Figure 11, the figure consists of four panels, A-D. However, the specification does not disclose which data is presented in its corresponding panel (pgs 20-21, joining ¶).

With respect to Figure 13, the figure consists of two panels, A-B, wherein the specification discloses the data presented in the corresponding panels as "right panel" and "left panel". (pg 21, lines 18-23) However, there are no "right" or "left" panels. It would be remedial to correctly identify each panel in the Brief Description of the Drawings by their corresponding Figure titles, specifically Figure 13A and Figure 13B.

Claim Objections

2. **Claims 1 and 21 are objected to because of the following informalities**:

With respect to claim 1, the word "different" (line 3) should be placed after, not before "two", as in "at least two different agents".

With respect to claim 21, the claim recites one of the agents is "tannic acid". However, "tannic acid" is recited in the base claim 1, and thus the recitation in claim 21 is redundant.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. **Claims 1-2, 4-7, 9-24, 43-44, 46 and 48-50 stand and 61-62 are newly rejected under 35 U.S.C. 112, first paragraph,** as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claimed invention is directed to a method for enhancing recombinant adeno-associated virus (rAAV) transduction of a mammalian cell. At issue for the purpose of written description requirements, are a) the identity and structure of the agent that "alters cellular uptake of rAAV", and b) the identity and structure of the agent that "modulates rAAV processing in the cell". It is noted that with respect to Claim 4, the recited agent that alters cellular uptake of rAAV is an undisclosed third agent to be used in the claimed method, wherein the elected first and second agents are DOXIL® and LLnL.

When the claims are analyzed in light of the specification, instant invention recites/encompasses a genus of structurally diverse compositions that are known in the art to possess mechanistically distinct biochemical activities. The lack of written support in the specification regarding the biological function possessed by each contemplated composition so as to be used in the instantly claimed method will be addressed presently.

> *Vas-cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not clearly allow persons of ordinary skill in the art to recognize that (he or she) invented what is claimed." (See *Vas-cath* at page 1116).

With respect to agents capable of altering the cellular uptake of rAAV, in analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, DOXIL® is the only species whose complete structure is disclosed to perform such functions. Next, then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e. other than nucleotide sequence), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, no other identifying characteristics identify *a priori* an agent that would perform the claimed function.

With respect to agents capable of modulating rAAV processing in the cell, in analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, LLnL, a proteosome inhibitor, is the only species whose complete structure is disclosed to perform such functions. Next, then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e. other than nucleotide sequence), specific features and functional attributes that would distinguish

different members of the claimed genus. In the instant case, no other identifying characteristics identify *a priori* an agent that would perform the claimed function.

The specification does not disclose any identifying characteristic as to how an artisan would have differentiated a first agent from any other second or third agent so as to alter the cellular uptake of rAAV or modulate intracellular viral processing. It is noted that all these agents vary greatly in structure and function and therefore each represents a subgenus. Again, the members of any of the subgenuses themselves would have very different structure and the specification does not provide any description of any identifying characteristics of the species of the subgenuses

The Revised Interim Guidelines state:

"The claimed invention as a whole may not be adequately described if the claims require an essential or critical element which is not adequately described in the specification and which is not conventional in the art" (col. 3, page 71434), "when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus", "in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus" (col. 2, page 71436).

An Applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

Possession may also be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the Applicant was in possession of the claimed invention. See, e.g., *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 1 19 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998), *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997)*, *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it").

Therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. See *Fiers v. Revel*, 25 USPQ2d 1602 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. *In Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

The two species of agents specifically disclosed to perform the claimed functions, DOXIL® and LLnL, are not representative of the genus of agents having distinctly different cell biological activities because the genus is highly variant. Accordingly, given that the specification does not teach what is the complete structure of a single species of the exceptionally broadly-defined "agent" genus that is explicitly disclosed to perform the recited functions, specifically i) alter cellular uptake of rAAV, and ii) modulate rAAV processing in the cell, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that the Applicant is in possession of the required starting materials to perform the necessary active steps and effect the claimed method, at the time the application was filed.

Thus, for the reasons outlined above, it is concluded that the claims do not meet the requirements for written description under 35 U.S.C. 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Applicant's Arguments

Applicant argues that:

a) neither Doxil nor LLnL are disclosed as being capable of altering the uptake of rAAV at the cell membrane;

b) other agents useful in the methods are disclosed in the specification;

c) Duan et al (2000) taught methods to determine whether an agent alters cellular membrane uptake of AAV and whether an agent alters rAAV processing in the cell; and

d) to provide an adequate written description for a claimed genus, the specification can provide a sufficient description of a representative number of species by an actual reduction to practice, reduction to drawings or by a disclosure of relevant, identifying characteristics, i.e., by a structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics (Guidelines for Examination of Patent Applications under the 35 U.S.C. § 112(1) Written Description Requirement, Fed. Reg., 66, 1099 (2001)).

Applicant's argument(s) has been fully considered, but is not persuasive.

With respect to a), Applicant has elected the agent interaction effect species "ii), wherein the agent alters cellular uptake of rAAV", and the biological functionality species "doxil" and "LLnL". Thus, if neither Doxil nor LLnL are capable of altering the uptake of rAAV at the cell membrane, then what is the agent that is to be applied to perform this function?

With respect to b), in the absence of explicitly pointing out where (page, line) the limitations are taught, the instant argument is incomplete and unpersuasive. Where in the specification is there a clear correspondence between the identity of an agent and the biological function recited in the claims?

With respect to c), an adequate written description of a chemical invention also requires a precise definition, such as by structure, formula, chemical name, or physical properties, and not merely a wish or plan for obtaining the chemical invention claimed. See, e.g., *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004) (The patent at issue claimed a method of selectively inhibiting PGHS-2 activity by administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product, however the patent did not disclose any compounds that can be used in the claimed methods. While there was a description of assays for screening compounds to identify those that inhibit the expression or activity of the PGHS-2 gene product, there was no disclosure of which peptides, polynucleotides, and small organic molecules selectively inhibit PGHS-2. The court held that "[w]ithout such disclosure, the claimed methods cannot be said to have been described."). In the instant case, while Duan et al may have taught a method to identify agents, the method of identifying such compounds does not immediately describe a compound's structural identity that would sufficiently distinguish it from any other structure that does not possess the required functional property.

With respect to d), unfortunately for Applicant, and the substantive issue discussed in the prior Office Action and iterated above, is that the functional characteristic(s) of each agent **has not** been coupled with a known or disclosed correlation between function and structure. Nor does the specification provide a sufficient description of a representative number of species by an actual reduction to practice.

4. **Claims 1-2, 4-7, 9-24, 43-44, 46 and 48-50 stand and 61-62 are newly rejected under 35 U.S.C. 112, first paragraph**, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention. If not, whether an

artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (*In re Wands*, 858 F.2d 731, 737, 8 USPQ2ds 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification. Therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention. And thus, skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The Breadth of the Claims and The Nature of the Invention

The breadth of the claim is exceptionally large for encompassing methods of enhancing the transduction of an enormous genus of recombinant adeno-associated viruses (rAAV) to an enormous genus of mammalian cells (both organisms and physiological cell types), wherein the transduction may occur *in vitro*, *ex vivo* or *in vivo*, the method comprising the use of an enormous genus of structurally diverse agents recited to perform a broad genus of distinctly different cell biological effects so as to enhance rAAV transduction in the target cell. Applicant broadly contemplates the term 'viral transduction' to include a broad genus of distinctly different and mutually exclusive cell biological processes, such as endocytosis, trafficking and processing of the rAAV through intracellular compartment(s), e.g., endosomal compartments, decreased viral nucleic acid or protein degradation, increased viral uncoating, or increased nuclear transport of virus or the viral genome, agents that interact with cytoskeletal elements, e.g., microtubules or microfilaments (pg 8, lines 23-27).

The inventive concept in the instant application is that rAAV transduction of a mammalian host cell may be enhanced by administering one or more compounds, e.g. the proteosome inhibitor LLnL or the antibiotic/chemotherapeutic compound contained in DOXIL®.

The State of the Prior Art, The Level of One of Ordinary Skill and The Level of Predictability in the Art

The level of one of ordinary skill in the art of recombinant adeno-associated viral vector design and delivery is considered to be high.

The prior art teaches that most viral gene delivery systems utilized to date have demonstrated significant limitations in practicality and safety due to the level and duration of recombinant transgene expression as well as their induction of host immunogenicity to vector proteins. (Kapturczak et al, Curr. Mol. Med. 1:245-258, 2001; pg 245, Abstract). The principal historical limitation of this vector system, efficiency of rAAV-mediated transduction, has been addressed by efforts to improve the titer, purity, and production capacity of rAAV preparations. RAAV transduction in certain tissues has been limited by the paucity of its receptors on certain cell types (pg 250, col. 1, ¶1). However, innovations have been made with regard to directing rAAV to attach to alternative receptors. (pg 250, col. 2, ¶1). Detailed studies of the AAV capsid proteins have shown that certain sites within the capsid can be intentionally altered to incorporate

new targeting ligands. Theoretically, this procedure could be to target a wide variety of different receptors and thus substantially expand the cellular tropism.

Mah et al (Molecular Therapy 6(1):106-112, 2001) teach obstacles impairing the use of rAAV as gene therapy vectors include sub-therapeutic levels of transduction, which is affected by such factors as cellular receptor density, multiplicity of infection and the time of exposure to vector particles, and the ability to target the site of gene transfer (pg 106, col. 1, ¶1). To this end, Mah et al teach the conjugation of microspheres to rAAV vectors to retard the flow of the vector through the vasculature, thus resulting in increased exposure time of vector to target cells (pg 106, col. 2, lines 4-7).

The prior art is silent with respect to the administration of agents, particularly the elected embodiments DOXIL® and LLnL, to enhance rAAV transduction. The claimed methods recite the administration of agents to alter distinctly different cell biological processes to enhance transduction. However, Goncalves (Virology J. 2: 43; 17 pages, 2005) teaches that the events and processes that regulate the trafficking of AAV particles into the nucleus are still not fully understood (pg 5 of 17). An increasingly important area in the development of AAV as a vector concerns the engineering of altered cell tropisms to narrow or broaden rAAV-mediated gene delivery and to increase its efficiency in tissues refractory to AAV2 infection. Cells can be poorly transduced by prototype rAAV2 not only because of low receptor content but also owing to impaired intracellular virion trafficking and uncoating or single-to-double strand genome conversion. Thus, considering that these processes depend either directly or indirectly on capsid conformation, cell targeting strategies determine not only the cell type(s) with which the vector interacts but also critically affect the efficiency of the whole gene transfer process. (pg 7 of 17) Several of these approaches rely on the modification by chemical, immunological or genetic means of the AAV2 capsid structure endowing it with ligands that interact with specific cell surface molecules. Another route to alter rAAV tropism exploits the natural capsid diversity of newly isolated serotypes by packaging rAAV2 genomes into capsids derived from other human or non-human AAV isolates. To this end, up until now, most researchers employ hybrid *trans*-complementing constructs that encode *rep* from AAV2 whereas *cap* is derived from the serotype displaying the cell tropism of choice. For example, experiments published recently using rAAV2 genomes pseudotyped with coats from AAV6 and AAV8 revealed stunning gene transfer efficiencies when these vectors were administered alone at high doses or in combination with a blood vessel permeating agent.

It is noted that Yan et al (J. Virology 78(6):2863-2874, 2004; *of record) teach that doxorubicin is an inhibitor of proteosome proteolytic activity, specifically the chymotrypsin-like proteolytic activity of the 20S proteosome (pg 2864, col. 1, ¶2; pg 2873, col. 2, lines 1-3), which contradicts the agent elected species recited in Claims 43 and 60, wherein the doxorubicin and DOXIL® are recited to not be an inhibitor of proteosome proteolytic activity.

Duan et al (J. Clin. Invest. 105:1573-1587, 2000; *of record) teach that the administration of tripeptide protease inhibitors, e.g. LLnL, increase rAAV gene delivery (pg 1573, Abstract). However, this phenomena is not universal in that the proteosome inhibitor did not affect transduction of skeletal or cardiac muscle, indicating that tissue-specific ubiquitination of viral capsid proteins interfere with rAAV-2 transduction.

Given the limited teachings in the art regarding the co-administration of two or more compounds designed to specifically alter particular cell biological processes to intentionally enhance rAAV transduction of an enormous genus of mammalian cell types *in vitro*, *ex vivo* and *in vivo*, one of ordinary skill in the art would reasonably conclude that a high degree of unpredictability regarding an *a priori* determination that any specific compound will enhance viral transduction. It necessarily follows that the art recognizes significant unpredictability for any two agents to yield an additive interaction to enhance viral transduction. Furthermore, there is a clear contradiction between the art and the instant specification regarding the biochemical properties of the doxorubicin and DOXIL® as per the inhibition of proteosome proteolytic activity.

The Existence of Working Examples and The Amount of Direction Provided by the Inventor

The method steps of the invention require the artisan to administer one or more compounds (or agents), wherein each compound is capable of fulfilling a recited function, namely i) alter cellular uptake of rAAV, ii) modulate rAAV processing in the cell, and iii) processing in intracellular compartments. Applicant broadly contemplates the term viral transduction to include endocytosis, trafficking and processing of the rAAV through intracellular compartment(s), e.g., endosomal compartments, decreased viral nucleic acid or protein degradation, increased viral uncoating, or increased nuclear transport of virus or the viral genome, agents that interact with cytoskeletal elements, e.g., microtubules or microfilaments (pg 8, lines 23-27). However, neither the claims nor the specification disclose explicitly which compound performs the recited function(s). For example, method Claims 4 and 46 recite the limitation "cellular uptake of rAAV" in reference to a cellular function modified by exposure to a second (Claim 46) or third (Claim 4) agent. There is insufficient antecedent basis for this limitation in the claim. The specification fails to use the phrase 'cellular uptake'. Thus, it necessarily follows that the specification fails to disclose specific agent compositions that can perform the claimed function. Rather, the specification discloses the phrases 'viral uptake' and "AAV uptake' (pg 75, lines 18-21). However, there are no specifically disclosed agents that alter 'viral uptake' besides LLnL and EGTA (pg 72, lines 10-15) so as to apprise the artisan exactly what agent is to be administered to fulfill the method step limitation(s).

The lack of correlation in the specification regarding the particular cell biological activity(ies) affected by each contemplated agent necessarily fails to provide sufficient guidance to the artisan so as to perform the claimed method(s). In the instant case, Applicant has elected the agent structure species "DOXIL®" and "LLnL", and the agent function species "alters cellular uptake of rAAV" and "modulates rAAV processing in the cell". The specification discloses DOXIL® to be a chemotherapeutic agent (pg 79, line 20) and is disclosed to enhance rAAV transduction (pg 82, line 31). DOXIL® is the liposomal formulation of doxorubicin (pg 80, line 17) that is an approved antibiotic (pg 9, line 25) and chemotherapeutic agent (pg 79, line 20). The specification also discloses that "LLnL" is a proteosome inhibitor that can enhance transduction (pg 5, line 30), but acts at a point distal to (that is, after) virus binding and entry (pg 70, line 8). LLnL and doxorubicin synergistically enhance rAAV transduction *in vitro*, as measured by reporter gene expression 1000-fold, while individually, doxorubicin and LLnL enhanced rAAV reporter gene expression 100- and 10-fold, respectively (pg 12, lines 8-10).

However, the instantly elected embodiment is DOXIL®, not doxorubicin. It is noted that DOXIL® could not be confirmed to be bioavailable to cell culture cells (pg 80, lines 17-18; pg 82, lines 2-4), and that "intranasally DOXIL®-treated mice did better than the doxorubicin-treated animals" (pg 110, lines 17-19). Thus, one of ordinary skill in the art would reasonably conclude that the functional ability(ies) of DOXIL® are not identical to doxorubicin, limiting the context in which DOXIL® may be used in combination with another agent(s) to enhance rAAV transduction. The specification fails to disclose the in vitro, ex vivo or in vivo administration of DOXIL® with any other agent, e.g. the elected LLnL embodiment, to a mammalian target cell. Thus, it naturally follows that there is no evidence that the co-administration of DOXIL® with LLnL will yield a functional interaction so as to additively enhance rAAV transduction of mammalian cells.

The Examiner also notes that the newly amended claims, wherein the proteasome modulating agent is now claimed to inhibit proteasome protease activity, teach away from the originally filed disclosure that the agent may modulate the proteosome, but does not inhibit proteolytic activity of the proteosome (pg 7, lines 13-18).

The Quantity of Any Necessary Experimentation to Make or Use the Invention

Thus, the quantity of necessary experimentation to make or use the invention as claimed, based upon what is known in the art and what has been disclosed in the specification, will create an undue burden for a person of ordinary skill in the art to demonstrate that the administration of an enormous genus of structurally and functionally diverse compositions so as to affect a broad genus of distinctly different and mutually exclusive cell biological processes will yield an additive functional interaction so as to enhance rAAV transduction of enormous genus of mammalian cells (both organisms and physiological cell types), wherein the transduction may occur *in vitro*, *ex vivo* or *in vivo*.

The instant portion of the invention, as claimed, falls under the "germ of an idea" concept defined by the CAFC. The court has stated that "patent protection is granted in return for an enabling disclosure, not for vague intimations of general ideas that may or may not be workable". The court continues to say that "tossing out the mere germ of an idea does not constitute an enabling disclosure" and that "the specification, not knowledge in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement". (See Genentech Inc v. Novo NordiskA/S 42 USPQ2d 1001, at 1005). The claimed methods of enhancing rAAV transduction comprising contacting a mammalian cell with an enormous genus of structurally and functionally diverse compositions so as to affect a broad genus of distinctly different and mutually exclusive cell biological processes constitute such a "germ of an idea".

The courts have stated that reasonable correlation must exist between scope of exclusive right to patent application and scope of enablement set forth in patent application. 27 USPQ2d 1662 *Exparte Maizel*. In the instant case, in view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed.

Accordingly, the instant claims are rejected for failing to comply with the enablement requirement.

Applicant's Arguments

Applicant argues that:

a) it would not be undue experimentation for the artisan to screen for compounds having the instantly recited functions so as to be useful in the instantly claimed method;

b) substantial progress has been made in addressing AAV-related issues regarding therapeutic gene transfer;

c) there is no contradiction between Yan et al. and the present disclosure, as Yan et al disclose that doxorubicin interacts with the proteasome through a mechanism distinct from that of tripeptidyl aldehydes. Yan et al do refer to the work of others, which reported that doxorubicin inhibits proteasome activity in a manner similar to aclarubicin. However, the Examiner is requested to note that the present specification discloses that "proteosome modulating agents" do not include agents that inhibit the proteolytic activity of the proteosome, that doxorubicin may facilitate viral binding to the proteasome and/or subsequent transportation into the nucleus in contrast to proteasome inhibitors such as LLnL and Z-LLL, and that the combined use of agents that individually have different or overlapping properties that alter rAAV transduction, as well as agents with similar or identical properties, can result in an additive and/or synergistic effect (pages 7-9).

Applicant's argument(s) has been fully considered, but is not persuasive.

With respect to a), the claims embrace an enormous genus of agents, each possessing distinctly different structural and functional properties. The artisan would essentially have to experiment by trial and error each combinatorial permutation of compounds embraced by the claims and capable of performing the recited functions so as to essentially invent for themselves a method of enhancing rAAV transduction *in vitro*, *ex vivo* and *in vivo*. In view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed.

With respect to b), the claims embrace rAAV transduction *in vivo* and the instant specification does not disclose formulations of the enormous genus of structurally undisclosed agents identified only by their functional activity in a cell, wherein the at least two agents from

said enormous genus are used in an amount that together at least additively enhance rAAV transduction *in vitro*, *ex vivo* and in a patient. In view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed.

With respect to c), the specification does not clearly define and distinguish those "proteasome modulating agents" that do or do not inhibit proteasome proteolytic activity, and which art-recognized proteaseome modulating agents are or are not to be used in the inventive method.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his invention.

5. **Claims 1-2, 4-7, 9-24, 43-44, 46 and 48-50 stand and claims 61-62 are newly rejected under 35 U.S.C. 112, second paragraph**, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: the correlation between the identity and structural limitations of each composition/agent and the recited cellular effect achieved by that agent. Claims 1, 4, 43, 46 and 61 recite cellular functions achieved by one or more agents, but the identity of the agent that performs the function is not recited. Conversely, Claims 21 and 43 several agents, but the function each agent performs in the target cell so as to achieve the inventive method is not recited. Dependent claims are included in the basis of the rejection because although they recite and encompass the method of using one or more agents, they do not clarify the nature of which agent performs which activity.

Applicant's Arguments

Applicant argues that each agent alone enhances AAV transduction.

Applicant's argument(s) has been fully considered, but is not persuasive. The substantive issue is that claims recite a plurality of structurally distinct agents and a plurality of biological activities; however, the claims do not establish a clear nexus between each claimed agent and its corresponding claimed function.

6. **The prior rejection of Claims 21 and 43 under 35 U.S.C. 112, second paragraph, is withdrawn** in light of Applicant's amendments to remove the trademarked product, DOXIL®, from the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. **The prior rejection of Claims 1-2, 4-7, 9, 16, 18, 21-23 and under 35 U.S.C. 102(b)** as being anticipated by Duan et al (J. Clin. Invest. 105:1573-1587, 2000; *of record) **is withdrawn** in light of Applicant's amendment to the claim, wherein "food additive" was substituted with "tannic acid". Duan et al do not teach the use of tannic acid.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the Examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. **The prior rejection of Claims 1, 10-17 and 19-20 under 35 U.S.C. 103(a)** as being unpatentable over Duan et al (J. Clin. Invest. 105:1573-1587, 2000; *of record) and Englehardt (U.S. Patent 6,436,392) **is withdrawn** in light of Applicant's amendment to the claim, wherein "food additive" was substituted with "tannic acid". Duan et al do not teach the use of tannic acid.

9. **The prior rejection of Claims 1 and 24 under 35 U.S.C. 103(a)** as being unpatentable over Duan et al (J. Clin. Invest. 105:1573-1587, 2000; *of record), Englehardt (U.S. Patent 6,436,392; *of record) and Hirsch et al (US 2003/0003583) **is withdrawn** in light of Applicant's amendment to the claim, wherein "food additive" was substituted with "tannic acid". Duan et al do not teach the use of tannic acid.

10. **Claims 43-44, 46, 48-50 and 54 are newly rejected under 35 U.S.C. 103(a)** as being unpatentable over Duan et al (J. Clin. Invest. 105:1573-1587, 2000; *of record) in view of

Kiyomiya et al (Cancer Res. 61:2467-2471, 2001; *of record in IDS) **is withdrawn** in light of Applicant's amendment to the claim, wherein the second agent enhances AAV transduction after viral binding to the cellular membrane and before second-strand synthesis.

11. **Claims 1-2, 4-7, 9-23, 43-44, 46, 48-50 and 61 are rejected under 35 U.S.C. 103(a)** as being unpatentable over Duan et al (J. Clin. Invest. 105:1573-1587, 2000; *of record) in view of Kiyomiya et al (Cancer Res. 61:2467-2471, 2001; *of record in IDS), Maitra et al (Am. J. Physiol. Cell Physiol. 280:C1031-C1037, 2001) and Englehardt (U.S. Patent 6,436,392; *of record).

Determining the scope and contents of the prior art.

Duan et al teach a method of enhancing adeno-associated virus 2 (rAAV-2) transduction, the method comprising contacting human lung cells with rAAV and at least two different agents, wherein one of the agents, specifically, the tripeptide protease inhibitor LLnL, inhibits proteosome proteolytic activity, wherein at LLnL modulates rAAV processing in the cell (pg 1582, col. 1, lines 5-7; col. 2, lines 15-17). LLnL enhances AAV transduction after viral binding to the cellular membrane and before second strand synthesis (pg 1581, col. 1). The AAV vector comprises a marker gene, specifically Green Fluorescent Protein (GFP) (pg 1574, Methods, see also references cited therein). The cells were pretreated with the proteosome protease inhibitors prior to contact with the rAAV (pg 1575, col. 2, Transduction). Duan et al also teach that the administration of LLnL after the cells are contacted with the virus also results in enhanced transgene expression (pg 1580, col. 2).

Duan et al do not teach the method to comprise the use of the agent doxorubicin. However, at the time of the invention, Kiyomiya et al taught that adriamycin (a synonym for doxorubicin) is a proteasome protease inhibitor.

Duan et al do not teach the method further comprising a second rAAV comprising a first DNA segment comprising a 5' ITR linked to a second DNA segment comprising a heterologous DNA which has sequences that are different than the sequences in the second DNA segment of the first recombinant DNA molecule linked to a third DNA segment comprising a 3' ITR. However, at the time of the invention, Englehardt disclosed methods of transducing mammalian

cells comprising at least two different rAAV vectors, wherein the second DNA segment comprising a heterologous sequence of the first vector is different from the second DNA segment comprising a heterologous sequence of the second vector. Englehardt disclosed wherein the second DNA segment of the first recombinant DNA molecule comprises a portion of an open reading frame for a gene product, optionally operably linked to at least one transcriptional regulatory element, and a splice donor site 3' to the portion of the open reading frame, and wherein the second DNA segment of the second recombinant DNA molecule comprises a splice acceptor site 5' to the remainder of an open reading frame, which together with the second DNA segment of the first recombinant DNA molecule encodes a functional gene product, substantially as claimed (col. 4, line 47-col. 5, line 25), wherein the transcriptional regulatory element comprises a promoter and an enhancer (col. 16, lines 1-6), and wherein the functional gene product is a therapeutic polypeptide, e.g. cystic fibrosis transmembrane conductance regulator (CFTR) (col. 3, line 30; col. 49, lines 23-48). Englehardt disclosed that the rAAV vectors form heteroconcatamers, which increased persistence of transgene expression, and thereby enhances the expression of the functional gene product (col. 3, lines 39-41; col. 10, lines 24-26).

Ascertaining the differences between the prior art and the claims at issue, and Resolving the level of ordinary skill in the pertinent art.

People of the ordinary skill in the art will be highly educated individuals such as medical doctors, scientists, or engineers possessing advanced degrees, including M.D.'s and Ph.D.'s. Thus, these people most likely will be knowledgeable and well-read in the relevant literature and have the practical experience in molecular biology, virology, cellular infection with rAAV, and protocols and reagents useful for the treatment of disease. Therefore, the level of ordinary skill in this art is high.

Duan et al teach that differentiated airway epithelia are extremely resistant to rAAV infection, thereby inhibiting therapeutic gene delivery of wildtype CFTR genes. The ubiquitin-proteasome pathway is involved in rAAV-2 transduction, and that when proteasome function was inhibited, a substantial augmentation in rAAV-2 mediated transgene expression was observed. Proteasome systems are known to modulate the intracellular processing of many foreign molecules, including viruses. LLnL substantially increased rAAV transduction from the

mucosal surface (Duan et al; pg 1579, col.s 1-2, joining ¶). Kiyomiya et al teach that doxorubicin is also a proteasome protease inhibitor. Maitra et al teach that low-dose doxorubicin significantly increases the functional cell-surface expression of CFTR and the most common CFTR mutation, DeltaF508. Restoration of functional CFTR expression to 10% of normal levels would be sufficient to ameliorate the symptoms of the disease *in vivo* (pg C1031, col. 20). Thus, administration of doxorubicin would be reasonably expected to achieve two therapeutic mechanisms in the treatment of Cystic Fibrosis, namely increased expression of CFTR to ameliorate the symptoms of the disease and enhance the rAAV viral transduction as per inhibition of the proteasome protease.

Neither Duan et al, Kiyomiya et al nor Maitra et al teach the formulations of doxorubicin and LLnL to achieve an additive or synergistic enhancement of rAAV transduction. However, it is well within the skill of the ordinary artisan to vary the respective concentrations of the first and second agents as part of routine optimization so as to identify conditions that would result in additive or synergistic enhancement by at least 2-fold to at least 10-fold relative to transduction of a correrresponding mammalian cell contacted with the rAAV and one of the agents or no agent, as demonstrated by Duan et al (pg 1576, Figure 5).

Duan et al do not teach the rAAV express a therapeutic or prophylactic gene product; however, Duan et al teach that AAV vectors are known in the art as a gene therapy vehicle and have been used in strategies conceived for functional correction of the cystic fibrosis transmembrane conductance regulator (CFTR; pg 1573, col. 1, Introduction). Absent evidence to the contrary, nothing non-obvious is seen with substituting the marker gene for a therapeutic or prophylactic gene in an AAV vector because the art has long recognized and used AAV vectors for gene therapy.

Considering objective evidence present in the application indicating obviousness or nonobviousness.

It would have been obvious to one of ordinary skill in the art to try combining the proteasome inhibitor LLnL with doxorubicin with a reasonable chance of success because a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this lead to the anticipated success, it is likely the product not of innovation, but of

ordinary skill and common sense. An artisan would be motivated to try combining doxorubicin with LLnL because Duan et al teach that continuous administration of LLnL is toxic to cells (pg 1580, col. 2). However, the use of an antibiotic recognized in the art to be a proteasome inhibitor in combination with LLnL may allow the artisan to use lower doses of LLnL yet still inhibit the proteasome, thereby providing enhanced viral transduction in the absence of toxic side effects. Furthermore, Maitra et al suggest using doxorubicin to increase the expression of CFTR, thereby ameliorating the symptoms of diseased polarized epithelial cells (Maitra et al). Thus, the combination of doxorubicin and LLnL would reasonably be expected to cooperate in therapeutic treatment of polarized epithelial cells.

It would have been obvious to one of ordinary skill in the art to try combining the method of enhancing rAAV transduction as taught by Duan et al to further comprise contacting the cell with an agent that alters uptake of rAAV at the cell membrane with a reasonable chance of success because a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this lead to the anticipated success, it is likely the product not of innovation, but of ordinary skill and common sense. Applicant admits that it is likely that EGTA altered AAV binding to cell surfaces or internalization (Remarks, pg 22, ¶2), and thus EGTA would be an art-recognized agent that alters uptake of rAAV at the cell membrane. An artisan would be motivated to try combining the method of enhancing rAAV transduction as taught by Duan et al to further comprise contacting the cell with an agent, e.g. EGTA, that alters uptake of rAAV at the cell membrane because Duan et al taught that the combined use of EGTA with LLnL enhanced transduction by at least 10 fold more than either agent alone (pg 1576, Figure 5).

It also would have been obvious to one of ordinary skill in the art to substitute the rAAV vector(s) of Duan et al for the rAAV vectors taught by Englehardt with a reasonable chance of success because at the time of the invention, the art had long-recognized the ability to co-transfect mammalian cells with a mixed rAAV population comprising at least two different rAAV vectors. The simple substitution of one rAAV population for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. An artisan would be motivated to use an rAAV population comprising two at least two different rAAV vectors because a two-rAAV-vector system based on the prior knowledge in the art regarding the molecular structure of rAAV concatamers may greatly increase the usefulness of rAAV gene

therapy vectors for those genes, e.g. CFTR, whose cDNA barely fits into an rAAV vector and whose expression has been hampered by the inefficient promoter activity of the rAAV ITR.

Thus, the invention as a whole is *prima facie* obvious.

12. **Claim 62 is rejected under 35 U.S.C. 103(a)** as being unpatentable over Duan et al (J. Clin. Invest. 105:1573-1587, 2000; *of record) in view of Kiyomiya et al (Cancer Res. 61:2467-2471, 2001; *of record in IDS), Maitra et al (Am. J. Physiol. Cell Physiol. 280:C1031-C1037, 2001) and Englehardt (U.S. Patent 6,436,392; *of record), as applied to claims 1-2, 4-7, 9-23, 43-44, 46, 48-50 and 61 above, and in further view of Voinea et al (J. Cell. Mol. Med. 6(4):465-474, 2002).

Determining the scope and contents of the prior art.

Neither Duan et al, Kiyomiya et al, Maitra et al nor Englehardt teach the liposomal formulation of doxorubicin. However, at the time of the invention, Voinea et al taught the use of 'intelligent' liposomes for efficient delivery of drugs, specifically Doxil®, the sterically-stabilized liposomal formulation of doxorubicin (pgs 469-470, joining ¶).

Ascertaining the differences between the prior art and the claims at issue, and Resolving the level of ordinary skill in the pertinent art.

People of the ordinary skill in the art will be highly educated individuals such as medical doctors, scientists, or engineers possessing advanced degrees, including M.D.'s and Ph.D.'s. Thus, these people most likely will be knowledgeable and well-read in the relevant literature and have the practical experience in molecular biology, virology, cellular infection with rAAV, and protocols and reagents useful for the treatment of disease. Therefore, the level of ordinary skill in this art is high.

Considering objective evidence present in the application indicating obviousness or nonobviousness.

It would have been obvious to one of ordinary skill in the art to substitute doxorubicin for the liposomal formulation of doxorubicin with a reasonable chance of success because the simple substitution of one known element for another would have yielded predictable results to one of

ordinary skill in the art at the time of the invention. An artisan would be motivated to substitute doxorubicin for the liposomal formulation of doxorubicin because the liposomal formulation provides for decreased toxicity than the naked drug as well as longer circulation times. Furthermore, the artisan may add targeting moieties onto a liposomal formulation so as to further improve the targeting of doxorubicin to the desired cell type.

Thus, absent evidence to the contrary, the invention as a whole is *prima facie* obvious.

Conclusion

13. No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Kevin K. Hill, Ph.D. whose telephone number is 571-272-8036. The Examiner can normally be reached on Monday through Friday, between 9:00am-6:00pm EST.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Joseph T. Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kevin K. Hill, Ph.D./
Examiner, Art Unit 1633

/Joseph T. Woitach/
Supervisory Patent Examiner, Art Unit 1633